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Seven new loci associated with age-related macular degeneration

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Seven New Loci Associated with Age-Related Macular Degeneration

The AMD Gene Consortium

Abstract

Age-related macular degeneration (AMD) is a common cause of blindness in older individuals. To accelerate understanding of AMD biology and help design new therapies, we executed a collaborative genomewide association study, examining >17,100 advanced AMD cases and >60,000 controls of European and Asian ancestry. We identified 19 genomic loci associated with AMD with $p<5\times10^{-8}$ and enriched for genes involved in regulation of complement activity, lipid metabolism, extracellular matrix remodeling and angiogenesis. Our results include 7 loci reaching $p<5\times10^{-8}$ for the first time, near the genes *COL8A1/FILIP1L*, *IER3/DDR1*, *SLC16A8*, *TGFBR1*, *RAD51B*, *ADAMTS9/MIR548A2*, and *B3GALTL*. A genetic risk score combining SNPs from all loci displayed similar good ability to distinguish cases and controls in all samples examined. Our findings provide new directions for biological, genetic and therapeutic studies of AMD.

AMD is a highly heritable progressive neurodegenerative disease that leads to loss of central vision through death of photoreceptors[1,2]. In developed countries, AMD is the leading cause of blindness in those >65 years[3]. Genes in the complement pathway[4–11] and a region of chromosome 10 [12,13] have now been implicated as the major genetic contributors to disease. Association has also been demonstrated with several additional loci[14–20], each providing an entry-point into AMD biology and potential therapeutic targets.

To accelerate the pace of discovery in macular degeneration genetics, 18 research groups from across the world formed the AMD Gene Consortium in early 2010, with support from the National Eye Institute (Table 1, Supplementary Table 1, Supplementary Note). To extend the catalog of disease associated common variants, we first organized a meta-analysis of genomewide association scans (GWAS) – combining data for >7,600 cases with advanced disease (geographic atrophy, neovascularization, or both) and >50,000 controls. Each study was first subject to GWAS quality control filters (customized taking into account study specific features[21] as detailed in Supplementary Table 2) and standardized to the HapMap reference panel and statistical genotype imputation[22–25]. Results were combined through meta-analysis[26] and thirty-two variants representing loci with promising evidence of association were genotyped in an additional >9,500 cases and >8,200 controls (Supplementary Tables 1–3; summary meta-analysis results available online). Our overall analysis of the most promising variants thus included >17,100 cases and >60,000 controls.

Our meta-analysis evaluated evidence for association at 2,442,884 SNPs (Figure 1). Inspection of Q-Q plots (Supplementary Figure 1) and the genomic control value (λ_{GC}=1.06) suggest that unmodeled population stratification does not significantly impact our findings (Supplementary Table 4 for details). Joint analysis of discovery and follow-up

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studies[27] resulted in 19 loci reaching $p<5\times10^{-8}$ (Figure 1, Table 2, Supplementary Table 5). These 19 loci include all susceptibility loci previously reaching $p<5\times10^{-8}$, except the 4q12 gene cluster for which association was reported in a Japanese population. In addition, the set includes seven loci reaching $p<5\times10^{-8}$ for the first time.

We evaluated heterogeneity between studies using the I^2 statistic, which compares variability in effect size estimates between studies to chance expectations[28]. We observed significant (p<.05/19) heterogeneity only for loci near *ARMS2* (I^2=75.7%, $p<1\times10^{-6}$) and near *CFH* (I^2=85.4%, $p<1\times10^{-6}$). Although these two loci were significantly associated in every sample examined, the magnitude of association varied more than expected. To explore sources of heterogeneity, we carried out a series of sub-analyses: we repeated the genomewide meta-analysis adding an age-adjustment, separating neovascular (NV) and geographic atrophy (GA) cases, in men and women, and in European- and Asian-ancestry samples separately (Figure 3, Supplementary Figure 2). These sub-analyses of the full GWAS dataset did not uncover additional loci reaching $p<5\times10^{-8}$; furthermore heterogeneity near *CFH* and *ARMS2* remained significant in all sub-analyses (I^2>65%, p <.001). Consistent with previous reports[17,29,30], separate analysis of NV and GA cases showed *ARMS2* risk alleles preferentially associated with risk of NV (OR_{NV}=2.97, OR_{GA}=2.50, $p_{difference}$=.0008) whereas *CFH* risk alleles preferentially associated with risk of GA (OR_{NV}=2.34, OR_{GA}=2.80, $p_{difference}$=.0006). We also observed large differences in effect sizes when stratifying by ethnicity, with variants near *CFH* exhibiting stronger evidence for association among Europeans (p=.0000001) and those near *TNFRSF10A* among East Asians (p=.002). Potential explanations include differences in linkage disequilibrium between populations or differences in environmental or diagnostic factors that modify genetic effects.

Identifying the full spectrum of allelic variation that contributes to disease in each locus will require sequencing of AMD cases and controls. To conduct an initial evaluation of the evidence for multiple AMD risk alleles in the nineteen loci described here, we repeated genomewide association analyses conditioning on the risk alleles listed in Table 2. We then examined each of the 19 implicated loci for variants with independent association (at p<.0002, corresponding for an estimate of ~250 independent variants per locus). This analysis resulted in the identification of the previously well documented independently associated variants near *CFH* and *C2*/*CFB*[8,10,31,32] and of additional independent signals near *C3*, *CETP, LIPC, FRK/COL10A1*, *IER3/DDR1*, *RAD51B* (Supplementary Table 6). In four of these loci, the independently associated variants mapped very close (within <60kb) to the original signal. This shows each locus can harbor multiple susceptibility alleles, encouraging searches for rare variants that elucidate gene function in these regions[33,34].

To prioritize our search for likely causal variants, we examined each locus in detail (see LocusZoom[35] plots in Supplementary Figure 3) and investigated whether AMD risk alleles were associated with changes in protein sequence, copy number variation or insertion deletion polymorphisms. One quarter of associated variants altered protein sequence, either directly (N=2) or through linkage disequilibrium (r^2>.6; N=3) with a nearby non-synonymous variant (Supplementary Table 7). Some coding variants point to well-studied genes (*ARMS2*, *C3* and *APOE*) while others help prioritize nearby genes for further study. In chromosome 4q25, index SNP rs4698775 is in strong linkage disequilibrium (r^2=.88) with a potentially protein damaging variant in *CCDC109B*[36], a coiled coil domain containing protein that may be involved in the regulation of gene expression. In chromosome 6q22, index SNP rs3812111 is a perfect proxy for a coding variant in *COL10A1*, a collagen protein that could be important in maintaining the structure and function of the extra-cellular matrix. Interestingly, rs1061170 (NP_000177.2[CFH]:p.His402Tyr) was not in disequilibrium with rs10737680, the most strongly associated SNP in the *CFH* region but, instead, was tagged by a secondary and

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weaker association signal (Supplementary Tables 6&7). This is consistent with prior haplotype analyses of the locus[10,31,32,34,37].

We used publicly available data[38,39] to check whether any of our index SNPs might be proxies for copy number variants or insertion-deletion polymorphisms (indels), which are hard to directly interrogate with genotyping arrays. This analysis identified a single strong association (r^2=.99), between rs10490924, a coding variant in the *ARMS2* gene which is the peak of association in 10q26, and a 3′ UTR indel polymorphism associated with *ARMS2* mRNA instability[40]. Since index SNP rs10490924 is also in strong disequilibrium (r^2=.90) with a nearby SNP, rs11200638, that regulates *HTRA1*[41], our data does not directly answer whether *HTRA1* or *ARMS2* is the causal gene in this locus. Although a common deletion of the CFHR1 and CFHR3 genes has been proposed[42,43], there was only modest signal in this study which is likely due to linkage disequilibrium with our most significantly associated variants in the locus (r^2=.31 between rs10737680 and 1000 Genomes Project MERGED_DEL_2_6731) as previously suggested[34].

Using RNA-sequencing[44], we examined mRNA levels of 85 genes within 100 kb of our index SNPs in post-mortem human retina (Supplementary Table 8). Of 19 independent risk loci, three had no genes with expressed transcripts in either old or young retina. Two genes showed differential expression between post-mortem retina of young (ages 17–35) and elderly (ages 75 and 77) individuals: *CFH* (p=.009) and *VEGFA* (p=.003), both with increased expression in older individuals. Using previously published data[45], we also examined the expression of associated genes in fetal and adult retinal pigment epithelium (RPE). This revealed increased *C3* expression in adult RPE compared to fetal RPE (p=.0008). *CFH*, *VEGFA* and *C3* are thus up-regulated with aging, and their role in AMD may indicate an accelerated aging process. In addition to *C3* and *CFH*, all the complement genes with detectable expression in the retina or RPE experiments showed higher expression levels in older tissue.

To identify biological relationships among our genetic association signals, we catalogued the genes within 100kb of the variants in each association peak (r^2>0.8 with the index SNP listed in Table 1). Ingenuity Pathway Analysis (Ingenuity Systems, Redwood, CA) highlighted several biological pathways, particularly the complement system and atherosclerotic signaling, to be enriched in the resulting set of 90 genes (Table 3, Supplementary Table 9). To account for features of genomewide association studies (such as the different number of SNPs in each gene), we carried out two additional analyses. First, we repeated our analysis for 50 sets of 19 control loci drawn from the NHGRI GWAS catalog[46]. In these 50 control sets, Ingenuity enrichment p-values for the complement system and for atherosclerosis signaling genes were exceeded 16% and 32% of the time respectively (although these two specific pathways were never implicated in a control dataset). We also repeated our enrichment analyses using the INRICH tool[47], which is specifically designed for the analysis of genomewide association studies – but accesses a more limited set of annotations. The INRICH analyses showed enrichment for genes encoding collagen and extra-cellular region proteins (both with $p=10^{-5}$ and after adjustment for multiple testing p_{adjust}=.0006), complement and coagulation cascades (p=.0002, p_{adjust}=.03), lipoprotein metabolism (p=.0003, p_{adjust}=.04), and regulation of apoptosis (p=.0009, p_{adjust}=.09) (Supplementary Table 10).

To explore the connections between our genetic association signals, we tested for interaction between pairs of risk alleles – looking for situations where joint risk was different than expected based on marginal effects. This analysis resulted in 171 tests of interaction, of which 9 were nominally significant (p<.05, see Supplementary Table 11), consistent with chance expectations. The strongest observed interaction involved risk alleles at rs10737680

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(near *CFH*) and rs429608 (near *C2/CFB*), the only association that remained significant after adjusting for multiple testing (p=.000052, <0.05/171=.00029). Individuals carrying risk alleles at both these loci where at slightly higher risk of disease than expected.

The proportion of the variability in the risk of AMD that is due to genes, or heritability, has been estimated at 45–70% [2]. Estimating the proportion of disease risk explained by the susceptibility loci identified [48] depends greatly on the disease prevalence - which is difficult to estimate in our sample, as it includes cases and controls of different ages and collected through a variety of ascertainment schemes. Using a model that assumes an underlying normally distributed but unobserved disease risk score or liability[49], the nineteen loci described here account for between 10% (if AMD prevalence is close to 1%) and 30% (if AMD prevalence is closer to 10%) of the variability in disease risk (corresponding to 15–65% of the total genetic contribution to AMD). The variants representing the peak of association at loci previously reaching genomewide significance account for the bulk of this variability: the new loci identified here account for 0.5–1.0% of the total heritability of AMD whereas secondary signals at novel and known loci account for 1.5–3.0% of the total heritability.

We report here the most comprehensive genetic association study of macular degeneration yet conducted, involving 18 international research groups, and a large set of cases and controls. Our data reveal 19 susceptibility loci, including 7 loci reaching $p<5\times10^{-8}$ for the first time, nearly doubling the number of known AMD loci outside the complement pathway. Our results show some susceptibility alleles exhibit different association across ethnic groups and may be preferentially associated with specific subtypes of disease. As with other GWAS meta-analysis, differences in genotyping methods, quality control steps and imputation strategies between samples might have a minor effect in our results – future studies may document that more uniform approaches across larger sample sizes might uncover more signals. A conundrum of macular degeneration genetics remains that the loci identified to date contribute to both GA and NV, two different phenotypes of advanced disease. In our sample, subtype specific GWAS analyses considering GA or NV cases only did not identify additional loci. Consistent with observations for other complex diseases[39], the majority of common disease susceptibility alleles do not alter protein sequences and are not associated with insertions or deletions of coding sequence or with copy number variation. We expect that the loci identified here will provide an ideal starting point for studies of rare variation[33,34].

In contrast to most other complex diseases, a risk score combining information across our 19 loci, can distinguish cases and controls relatively well (Figure 4, area under the ROC curve [AUC]=.52 including only new loci or AUC=.74 including new and previously reported loci; Supplementary Figure 4). It may be possible to use similar scores to identify and prioritize at risk individuals so they receive preventative treatment prior to the onset of disease[50]. Monotherapies are increasingly utilized to manage neovascular disease, but offer only a limited repertoire of treatment options to patients. Identification of novel genes and pathways enables us to pursue a larger range of disease-specific targets for development of new therapeutic interventions. We expect that future therapies directed at earlier stages of the disease process will allow patients to retain visual function for longer periods, improving the quality of life for individuals with AMD.

ONLINE METHODS

GENOME-WIDE SCAN FOR LATE AMD ASSOCIATION INCLUDING FOLLOW-UP

Study-specific association analysis for discovery—Genotyping was performed on a variety of different platforms summarized in Supplementary Table 2. Each group

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submitted results from association tests using genotyped and imputed data where the allelic dosages were computed with either MACH[25], IMPUTE[23], BEAGLE[24], or snpStats[52] using the HapMap2 reference panels. The CEU panel was used as a reference for imputation-based analyses for most samples (predominantly of European ancestry), with two exceptions: for the JAREDS samples (predominantly of East Asian ancestry), the CHB+JPT panel was used as a reference; for the VRF samples (predominantly of South Asian ancestry) the combined CEU and CHB+JPT panels were used[22,53]. For most data sets association tests were run under a logistic regression model using either Plink[54], Mach2dat[25], ProbABEL[55], or snpStats[52], though for one dataset containing related individuals the generalized estimating equations algorithm[56] as implemented in R[57,58]. In addition to the primary analysis which tested for SNP associations with advanced AMD unadjusted for age, an age-adjusted sensitivity analysis was conducted by each group with available age. Each group also provided stratified results by sex or AMD subtype (GA or NV) as long as the sample size per stratum exceeded 50 subjects. For all analyses, study-specific control for population stratification was conducted (Supplementary Table 4).

Study-specific association analysis for follow-up—Genotyping of the selected SNPs was performed on different platforms; the same models, sensitivity and stratified analyses were computed by each follow-up partner, while SNPs with insufficient call rate were excluded based on study-specific thresholds. If the index SNP could not be genotyped, a highly correlated proxy was used whenever possible (Supplementary Tables 2&3).

Quality control before meta-analysis—Before meta-analysis, all study-specific files underwent quality control procedures to check for completeness and plausible descriptive statistics on all variables as well as for compliance of allele frequencies with HapMap[59]. In addition, we excluded SNP results of a study into meta-analysis (i) for discovery: if imputation quality measures were too low (MACH & PLINK <0.3; SNPTEST <0.4) or if effect sizes (|beta|) or standard errors were too extreme (5) indicating instability of the estimates, (ii) for follow-up: if Hardy-Weinberg equilibrium was violated (p<0.05/32).

Meta-analyses—For both discovery and follow-up, we performed meta-analyses using the inverse variance weighted fixed effect model, which pools the effect size and standard error of each participated GWAS. Using an alternative weighted z-score method, which is based on a weighted sum of z-score statistics, we obtained a very similar set of test statistics (correlation of −log10(p-value) >0.98). All analyses were performed using METAL[26] and R. For the discovery, we applied two rounds of genomic control corrections to each individual GWAS and the combined meta results, respectively [51]. All results were analyzed and validated among four independent teams.

EXTENDED ANALYSES FOR THE IDENTIFIED AMD LOCI

Extended analyses were conducted on the identified loci and particularly on the top SNP of each locus.

Second signal analysis—To detect potential independent signals within the identified AMD loci, each study partner with genotypes for all identified SNPs available re-analyzed their data for all SNPs in the respective loci (index SNP ±1Mb) using a logistic regression model containing all identified index SNPs. Quality control procedures were performed as before. The beta estimates for each SNP were meta-analyzed applying the effective sample size weighted z-score method and two rounds of genomic control correction. The significance threshold (p<0.05) for an independent association signal within any of the identified loci was Bonferroni-adjusted using the average effective number of SNPs

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involved across the identified loci determined by SNPSpD[60]. To this analysis, 13 studies contributed including 7,489 cases and 51,562 controls.

Interaction analysis—Utilizing a pre-specified R-scripts (see URLs), GWAS partners performed 171 logistic regression analyses modeling the pair-wise interaction of the 19 index SNPs assuming an additive model for main and interaction effects. Study-specific covariates were included to the model if required. Per study, quality control included a check for consistency of SNP main effects between discovery and interaction analysis. SNPs with low imputation quality measures and pairs with |beta|>5 or standard errors >5 were excluded before meta-analyzing the interaction effects with the inverse variance weighted fixed effect model in METAL. To this analysis, 12 studies contributed including 6,645 cases and 49,410 controls.

GENETIC RISK SCORE

The meta-analyzed effect sizes, β_j, for each of the 19 SNPs were calculated in the meta-analysis described above and normalized: $\widehat{\beta}_j=\beta_j/\sum_{k=1}^{19}\beta_k$, j=1,…,19. Using these as weights, each study partner with all 19 SNPs available computed the individuals' genetic risk score as a normalized weighted sum of the AMD risk increasing alleles among the identified SNPs as

$$S_i=\sum_j \widehat{\beta}_j x_{ij},$$

where x_{ij} is the genotype of the ith individual at the jth SNP, so S_i ranges from 0 to 2. This data was available from 12 studies including 7,195 cases and 49,149 controls.

For each study, we used a leave-one-out cross-validation to access the prediction of the risk score. For the kth subject, we fitted a logistic regression model from all subjects in the study excluding the kth subjects: $\log(\frac{y_i}{1-y_i})=\alpha+\gamma S_i$, $i! = k$, α is the intercept and γ is the effect of the genetic risk score. The fitted probability of the kth subject was then estimated as $\hat{y}_k = 1/(1+e^{-(\hat{\alpha}+\hat{\gamma}S_k)})$. We sorted the fitted probabilities and calculated sensitivity and specificity by varying the risk threshold (the value compared with the fitted probability to dichotomize the subject into case or control) from 0 to 1. These were utilized to compute the area-under-the curve (AUC) of the receiver-operating-curve (ROC).

IDENTIFICATION OF CORRELATED CODING VARIANTS AND TAGGED NON-SNP VARIATION

LD estimates were calculated using genotype data of the identified risk loci (index SNPs ±500kb) of individuals with European ancestry from the 1000 Genomes Project (March 2012 release)[61] or from HapMap (release #28)[59]. Variants correlated (r^2>0.6) with one of the GWAS index SNPs were identified using PLINK[54]. To filter coding variants, all correlated variants were mapped against RefSeq transcripts using ANNOVAR[62].

GENE EXPRESSION

We evaluated expression of genes within 100kb of one of the 19 index SNPs, as well as of several retina-specific, RPE-specific and housekeeping genes unrelated to AMD for comparison in retina (RNA-sequencing data from three young [17–35 yrs age] and two old

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individuals [75 and 77 yrs age]) as well as in fetal and adult retinal pigment epithelium (RPE; published data in the Gene Expression Omnibus database[45]). Expression was analyzed using previously described protocols[44] (Supplementary Table 8).

PATHWAY ANALYSES

Functional enrichment analysis was performed using the Ingenuity Pathway Analysis software (IPA, Ingenuity® Systems). Any gene located within 100kb of a SNP in high LD (r^2>0.8) with one of the index SNPs was considered a potential AMD risk associated gene and considered for subsequent pathway enrichment analysis. LD estimates were calculated as described above. Applying the above inclusion filters, 90 genes appear to be implicated by our 19 replicated AMD SNPs (Supplementary Table 8). Because genes with related function sometimes cluster in the same locus, we trimmed gene lists during analysis so that only one gene per locus was used to evaluate enrichment for each pathway. The P-value of the association between our implicated gene list and any of the canonical pathways and/or functional gene sets as annotated by IPA's Knowledge Base was computed using a one-sided Fisher's exact test. The Benjamini-Hochberg method was used to estimate False Discovery Rates. To evaluate significance of observed enrichment, we repeated our Ingenuity analysis starting with 50 lists of 19 SNPs randomly drawn from the NHGRI GWAS catalog[46] and, again, using the INRICH tool[63]. When using INRICH, we used gene sets defined in the Broad's Molecular Signatures database[47] (ver3.0) representing manually curated canonical pathway, Gene Ontology biological process, cellular component and molecular function gene sets (C2:CP, C5:BP, C5:CC and C5:MF). We provided INRICH with our full GWAS SNP list and allowed it to carry out 100,000 permutations, matching selected loci in terms of gene count, SNP density and total number of SNPs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Swaroop A, Chew EY, Rickman CB, Abecasis GR. Unravelling a Late-Onset Multifactorial Disease: From Genetic Susceptibility to Disease Mechanisms for Age-related Macular Degeneration. Annu Rev Genomics Hum Genet. 2009; 10:19–43. [PubMed: 19405847]
2. Seddon JM, Cote J, Page WF, Aggen SH, Neale MC. The US twin study of age-related macular degeneration: relative roles of genetic and environmental influences. Archives of Ophthalmology. 2005; 123:321–7. [PubMed: 15767473]
3. Friedman DS, et al. Prevalence of age-related macular degeneration in the United States. Archives of Ophthalmology. 2004; 122:564–72. [PubMed: 15078675]

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4. Edwards AO, et al. Complement factor H polymorphism and age-related macular degeneration. Science. 2005; 308:421–4. [PubMed: 15761121]
5. Haines JL, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science. 2005; 308:419–21. [PubMed: 15761120]
6. Klein RJ, et al. Complement factor H polymorphism in age-related macular degeneration. Science. 2005; 308:385–9. [PubMed: 15761122]
7. Yates JR, et al. Complement C3 variant and the risk of age-related macular degeneration. N Engl J Med. 2007; 357:553–61. [PubMed: 17634448]
8. Gold B, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat Genet. 2006; 38:458–62. [PubMed: 16518403]
9. Fagerness JA, et al. Variation near complement factor I is associated with risk of advanced AMD. Eur J Hum Genet. 2009; 17:100–4. [PubMed: 18685559]
10. Hageman GS, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U S A. 2005; 102:7227–32. [PubMed: 15870199]
11. Maller JB, et al. Variation in complement factor 3 is associated with risk of age-related macular degeneration. Nat Genet. 2007; 39:1200–1. [PubMed: 17767156]
12. Rivera A, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. Hum Mol Genet. 2005; 14:3227–36. [PubMed: 16174643]
13. Jakobsdottir J, et al. Susceptibility genes for age-related maculopathy on chromosome 10q26. Am J Hum Genet. 2005; 77:389–407. [PubMed: 16080115]
14. Klaver CC, et al. Genetic association of apolipoprotein E with age-related macular degeneration. American Journal of Human Genetics. 1998; 63:200–6. [PubMed: 9634502]
15. Souied EH, et al. The epsilon4 allele of the apolipoprotein E gene as a potential protective factor for exudative age-related macular degeneration. American Journal of Ophthalmology. 1998; 125:353–9. [PubMed: 9512153]
16. McKay GJ, et al. Evidence of association of APOE with age-related macular degeneration: a pooled analysis of 15 studies. Human Mutation. 2011; 32:1407–16. [PubMed: 21882290]
17. Chen W, et al. Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:7401–6. [PubMed: 20385819]
18. Neale BM, et al. Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (LIPC). Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:7395–400. [PubMed: 20385826]
19. Yu Y, et al. Common variants near FRK/COL10A1 and VEGFA are associated with advanced age-related macular degeneration. Human Molecular Genetics. 2011; 20:3699–709. [PubMed: 21665990]
20. Arakawa S, et al. Genome-wide association study identifies two susceptibility loci for exudative age-related macular degeneration in the Japanese population. Nature Genetics. 2011; 43:1001–4. [PubMed: 21909106]
21. McCarthy MI, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genet. 2008; 9:356–69. [PubMed: 18398418]
22. Li Y, Willer CJ, Sanna S, Abecasis GR. Genotype Imputation. Annu Rev Genomics Hum Genet. 2009; 10:387–406. [PubMed: 19715440]
23. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. Nature Genetics. 2007; 39:906–13. [PubMed: 17572673]
24. Browning BL, Browning SR. A unified approach to genotype imputation and haplotype-phase inference for large data sets of trios and unrelated individuals. American Journal of Human Genetics. 2009; 84:210–23. [PubMed: 19200528]
25. Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. Genetic Epidemiology. 2010; 34:816–34. [PubMed: 21058334]

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26. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010; 26:2190–1. [PubMed: 20616382]
27. Skol AD, Scott LJ, Abecasis GR, Boehnke M. Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. Nat Genet. 2006; 38:209–13. [PubMed: 16415888]
28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327:557–60. [PubMed: 12958120]
29. Sobrin L, et al. ARMS2/HTRA1 locus can confer differential susceptibility to the advanced subtypes of age-related macular degeneration. American Journal of Ophthalmology. 2011; 151:345–52. e3. [PubMed: 21122828]
30. Seddon JM, et al. Association of CFH Y402H and LOC387715 A69S with progression of age-related macular degeneration. JAMA. 2007; 297:1793–800. [PubMed: 17456821]
31. Li M, et al. CFH haplotypes without the Y402H coding variant show strong association with susceptibility to age-related macular degeneration. Nature Genetics. 2006; 38:1049–54. [PubMed: 16936733]
32. Maller J, et al. Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. Nature Genetics. 2006; 38:1055–9. [PubMed: 16936732]
33. Nejentsev S, Walker N, Riches D, Egholm M, Todd JA. Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes. Science. 2009; 324:387–9. [PubMed: 19264985]
34. Raychaudhuri S, et al. A rare penetrant mutation in CFH confers high risk of age-related macular degeneration. Nature Genetics. 2011; 43:1232–6. [PubMed: 22019782]
35. Pruim RJ, et al. LocusZoom: regional visualization of genome-wide association scan results. Bioinformatics. 2010; 26:2336–7. [PubMed: 20634204]
36. Adzhubei IA, et al. A method and server for predicting damaging missense mutations. Nat Methods. 2010; 7:248–9. [PubMed: 20354512]
37. Sivakumaran TA, et al. A 32 kb Critical Region Excluding Y402H in CFH Mediates Risk for Age-Related Macular Degeneration. PLoS ONE. 2011; 6:e25598. [PubMed: 22022419]
38. The Wellcome Trust Case Control Consortium. Genome-wide association study of CNVs in 16, 000 cases of eight common diseases and 3, 000 shared controls. Nature. 2010; 464:713–20. [PubMed: 20360734]
39. The 1000 Genomes Project. A map of human genome variation from population scale sequencing. Nature. 2010; 467
40. Fritsche LG, et al. Age-related macular degeneration is associated with an unstable ARMS2 (LOC387715) mRNA. Nat Genet. 2008; 40:892–6. [PubMed: 18511946]
41. Dewan A, et al. HTRA1 promoter polymorphism in wet age-related macular degeneration. Science. 2006; 314:989–92. [PubMed: 17053108]
42. Hughes AE, et al. A common CFH haplotype, with deletion of CFHR1 and CFHR3, is associated with lower risk of age-related macular degeneration. Nat Genet. 2006; 38:1173–7. [PubMed: 16998489]
43. Fritsche LG, et al. An imbalance of human complement regulatory proteins CFHR1, CFHR3 and factor H influences risk for age-related macular degeneration (AMD). Human Molecular Genetics. 2010; 19:4694–704. [PubMed: 20843825]
44. Brooks MJ, Rajasimha HK, Roger JE, Swaroop A. Next-generation sequencing facilitates quantitative analysis of wild-type and Nrl(–/–) retinal transcriptomes. Molecular Vision. 2011; 17:3034–54. [PubMed: 22162623]
45. Strunnikova NV, et al. Transcriptome analysis and molecular signature of human retinal pigment epithelium. Human Molecular Genetics. 2010; 19:2468–86. [PubMed: 20360305]
46. Hindorff LA, et al. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106:9362–7. [PubMed: 19474294]

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47. Subramanian A, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102:15545–50. [PubMed: 16199517]
48. Manolio TA, et al. Finding the missing heritability of complex diseases. Nature. 2009; 461:747–53. [PubMed: 19812666]
49. So HC, Gui AH, Cherny SS, Sham PC. Evaluating the heritability explained by known susceptibility variants: a survey of ten complex diseases. Genetic Epidemiology. 2011; 35:310–7. [PubMed: 21374718]
50. Seddon JM, Reynolds R, Yu Y, Daly MJ, Rosner B. Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors. Ophthalmology. 2011; 118:2203–11. [PubMed: 21959373]
51. Devlin B, Roeder K. Genomic control for association studies. Biometrics. 1999; 55:997–1004. [PubMed: 11315092]
52. Wallace C, et al. The imprinted DLK1-MEG3 gene region on chromosome 14q32.2 alters susceptibility to type 1 diabetes. Nature Genetics. 2010; 42:68–71. [PubMed: 19966805]
53. Huang L, et al. Genotype-imputation accuracy across worldwide human populations. American Journal of Human Genetics. 2009; 84:235–50. [PubMed: 19215730]
54. Purcell S, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007; 81:559–75. [PubMed: 17701901]
55. Aulchenko YS, Struchalin MV, van Duijn CM. ProbABEL package for genome-wide association analysis of imputed data. BMC Bioinformatics. 2010; 11:134. [PubMed: 20233392]
56. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986; 42:121–30. [PubMed: 3719049]
57. Carey, VJ. R package version 4.13–18. 2012. Ported to R by Thomas Lumley and Brian Ripley. Note that maintainers are not available to give advice on using a package they did not author. gee: Generalized Estimation Equation solver.
58. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing; Vienna, Austria: 2012.
59. The International HapMap Consortium et al. Integrating common and rare genetic variation in diverse human populations. Nature. 2010; 467:52–8. [PubMed: 20811451]
60. Nyholt DR. A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. Am J Hum Genet. 2004; 74:765–9. [PubMed: 14997420]
61. The 1000 Genomes Project Consortium et al. An integrated map of genetic variation from 1, 092 human genomes. Nature. 2012; 491:56–65. [PubMed: 23128226]
62. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res. 2010; 38:e164. [PubMed: 20601685]
63. Lee PH, O'Dushlaine C, Thomas B, Purcell SM. INRICH: interval-based enrichment analysis for genome-wide association studies. Bioinformatics. 2012; 28:1797–9. [PubMed: 22513993]

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Gene Expression and RNA-Sequencing Data: These data were contributed and analyzed by M.Br., J.S.F., N.G., R.R.P and A.S.

URLs

METAL, http://www.sph.umich.edu/csg/abecasis/Metal/; R, http://www.R-project.org/; gee, http://CRAN.R-project.org/package=gee; Single Nucleotide Polymorphism Spectral Decomposition, http://gump.qimr.edu.au/general/daleN/SNPSpDlite/; Pre-specified R-scripts, http://www.epi-regensburg.de/wp/genepi-downloads; The 1000 Genomes Project, http://www.1000genomes.org/; The HapMap Project, http://www.hapmap.org/genotypes/; PolyPhen-2, http://genetics.bwh.harvard.edu/pph2/; Ingenuity® Systems, http://www.ingenuity.com; NHGRI GWAS catalog, http://www.genome.gov/gwastudies/, INRICH, http://atgu.mgh.harvard.edu/inrich; Full Result Set, http://www.sph.umich.edu/csg/abecasis/public/amdgene2012/

CONFLICT OF INTEREST STATEMENT

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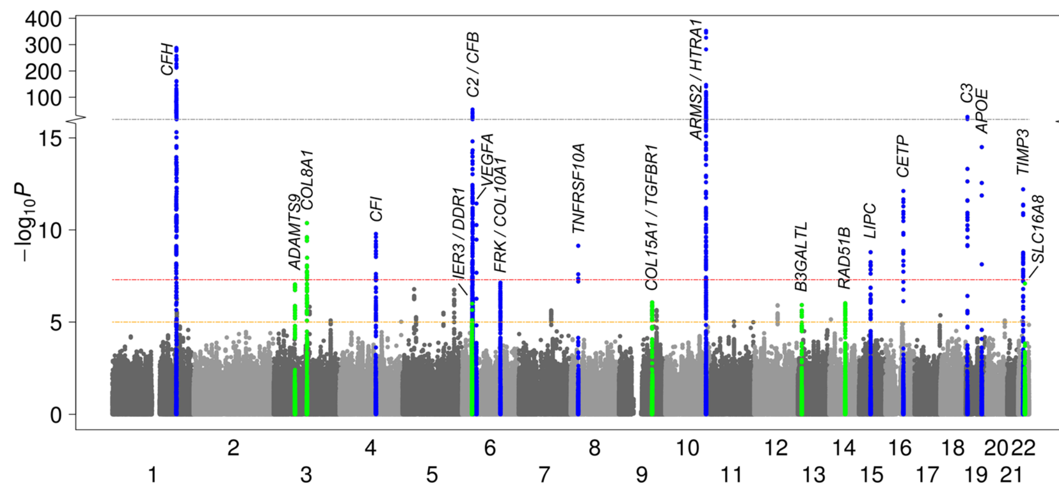

FIGURE 1. Summary of genomewide association scan results

Summary of genomewide association scan results in the discovery GWAS sample. Previously described loci reaching $p < 5\times10^{-8}$ are labeled in blue; new loci reaching $p < 5\times10^{-8}$ for the first time after follow-up are labeled in green.

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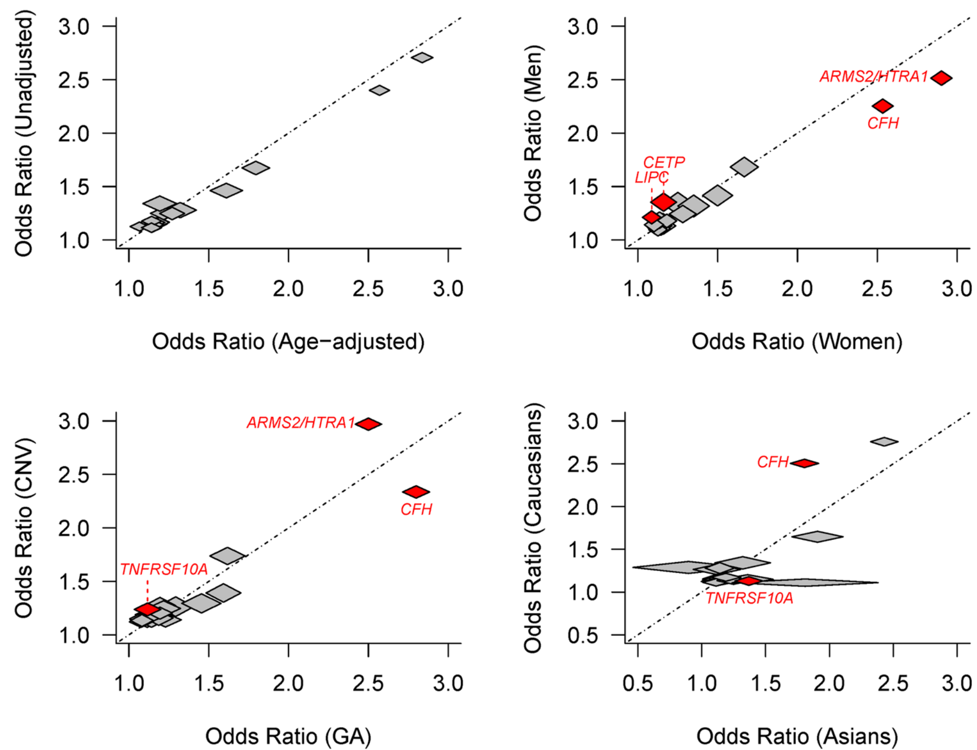

FIGURE 2. Sensitivity analysis

The top left panel compares estimated effect sizes for the original analysis and for an age-adjusted analysis (where age was included as a covariate and samples of unknown age were excluded). The top right panel compares analyses stratified by sex. The bottom left panel evaluates stratification by disease subtype. The bottom right panel evaluates stratification by ethnicity. The size of each marker reflects confidence intervals (with height reflecting confidence interval along the Y axis and width reflecting confidence interval along the X axis). Comparisons reaching $p < 0.05$ are labeled and colored in red.

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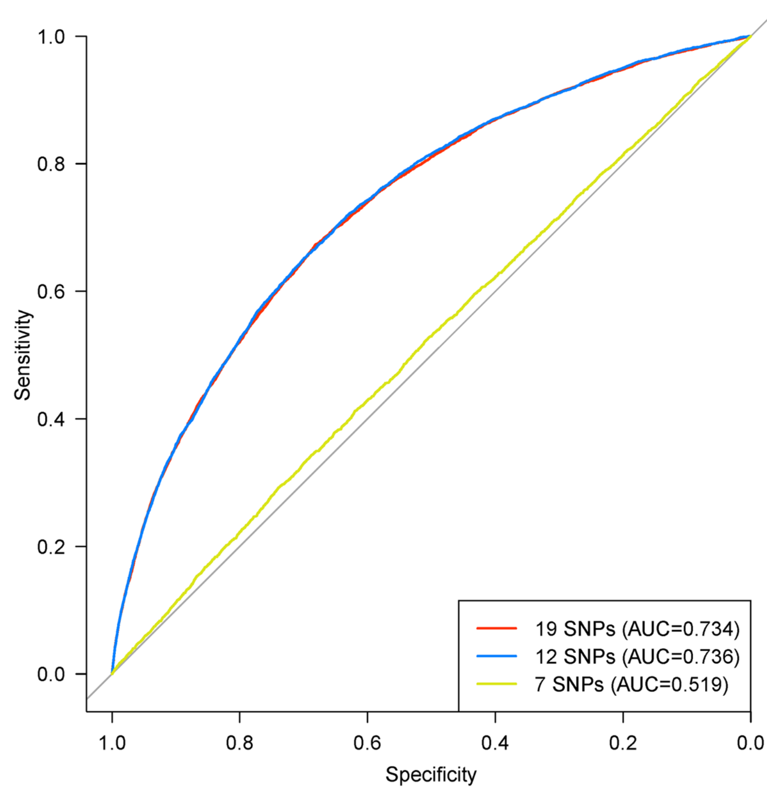

FIGURE 3. Risk score analysis

We calculated a risk score for each individual, defined as the product of the number of risk alleles at each locus and the associated effect size for each allele (measured on the log-odds scale). The plot summarizes the ability of these overall genetic risk scores to distinguish cases and controls.

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TABLE 1

Summary of the Samples Used in Genomewide Discovery and Targeted Follow-Up Analyses

For additional details, including a breakdown of the number of cases and controls in individual samples, see Supplementary Table 1. N_{CASES} includes only cases with geographic atrophy, choroidal neovasculartization, or both.

Analysis	Contributing Study Groups	N_{CASES}	%Female	%Neovascular Disease	$N_{CONTROLS}$	% Female
Genomewide Discovery	15	7,650	53.9	59.2	51,844	45.2
Targeted Follow-up	18	9,531	56.3	57.8	8,230	53.8
Overall	33	17,181	55.2	58.4	60,074	46.3

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TABLE 2

Summary of Loci Reaching Genome-Wide Significance

All results reported here include a genomic control correction for individual studies and also for the final meta-analysis[51].

SNP/Risk Allele	Chromosome	Position	Nearby Genes	EAF	Discovery		Follow-up		Joint		
					P	OR	*P*	OR	*P*	OR	95% CI
Loci Previously Reported With P < 5×10^−8^											
rs10490924/T	10	124.2 Mb	*ARMS2/HTRA1*	0.30	$4{\times}10^{-353}$	2.71	$2.8{\times}10^{-190}$	2.88	$4{\times}10^{-540}$	2.76	[2.72–2.80]
rs10737680/A	1	196.7 Mb	*CFH*	0.64	$1{\times}10^{-283}$	2.40	$2.7{\times}10^{-152}$	2.50	$1{\times}10^{-434}$	2.43	[2.39–2.47]
rs429608/G	6	31.9 Mb	*C2/CFB*	0.86	$2{\times}10^{-54}$	1.67	$2.4{\times}10^{-37}$	1.89	$4{\times}10^{-89}$	1.74	[1.68–1.79]
rs2230199/C	19	6.7 Mb	*C3*	0.20	$2{\times}10^{-26}$	1.46	$3.4{\times}10^{-17}$	1.37	$1{\times}10^{-41}$	1.42	[1.37–1.47]
rs5749482/G	22	33.1 Mb	*TIMP3*	0.74	$6{\times}10^{-13}$	1.25	$9.7{\times}10^{-17}$	1.45	$2{\times}10^{-26}$	1.31	[1.26–1.36]
rs4420638/A	19	45.4 Mb	*APOE*	0.83	$3{\times}10^{-15}$	1.34	$4.2{\times}10^{-7}$	1.25	$2{\times}10^{-20}$	1.30	[1.24–1.36]
rs1864163/G	16	57 Mb	*CETP*	0.76	$8{\times}10^{-13}$	1.25	$8.7{\times}10^{-5}$	1.17	$7{\times}10^{-16}$	1.22	[1.17–1.27]
rs943080/T	6	43.8 Mb	*VEGFA*	0.51	$4{\times}10^{-12}$	1.18	$1.6{\times}10^{-5}$	1.12	$9{\times}10^{-16}$	1.15	[1.12–1.18]
rs13278062/T	8	23.1 Mb	*TNFRSF10A*	0.48	$7{\times}10^{-10}$	1.17	$6.4{\times}10^{-7}$	1.14	$3{\times}10^{-15}$	1.15	[1.12–1.19]
rs920915/C	15	58.7 Mb	*LIPC*	0.48	$2{\times}10^{-9}$	1.14	0.004	1.10	$3{\times}10^{-11}$	1.13	[1.09–1.17]
rs4698775/G	4	110.6 Mb	*CFI*	0.31	$2{\times}10^{-10}$	1.16	0.025	1.08	$7{\times}10^{-11}$	1.14	[1.10–1.17]
rs3812111/T	6	116.4 Mb	*COL10A1*	0.64	$7{\times}10^{-8}$	1.13	0.022	1.06	$2{\times}10^{-8}$	1.10	[1.07–1.14]
Loci Reaching P < 5×10^−8^ for the First Time											
rs13081855/T	3	99.5 Mb	*COL8A1/FILIP1L*	0.10	$4{\times}10^{-11}$	1.28	$6.0{\times}10^{-4}$	1.17	$4{\times}10^{-13}$	1.23	[1.17–1.29]
rs3130783/A	6	30.8 Mb	*IER3/DDR1*	0.79	$1{\times}10^{-6}$	1.15	$3.5{\times}10^{-6}$	1.16	$2{\times}10^{-11}$	1.16	[1.11–1.20]
rs8135665/T	22	38.5 Mb	*SLC16A8*	0.21	$8{\times}10^{-8}$	1.16	$5.6{\times}10^{-5}$	1.13	$2{\times}10^{-11}$	1.15	[1.11–1.19]
rs334353/T	9	101.9 Mb	*TGFBR1*	0.73	$9{\times}10^{-7}$	1.13	$6.7{\times}10^{-6}$	1.13	$3{\times}10^{-11}$	1.13	[1.10–1.17]
rs8017304/A	14	68.8 Mb	*RAD51B*	0.61	$9{\times}10^{-7}$	1.11	$2.1{\times}10^{-5}$	1.11	$9{\times}10^{-11}$	1.11	[1.08–1.14]
rs6795735/T	3	64.7 Mb	*ADAMTS9/MIR548A2*	0.46	$9{\times}10^{-8}$	1.13	0.0066	1.07	$5{\times}10^{-9}$	1.10	[1.07–1.14]
rs9542236/C	13	31.8 Mb	*B3GALTL*	0.44	$2{\times}10^{-6}$	1.12	0.0018	1.08	$2{\times}10^{-8}$	1.10	[1.07–1.14]

See Supplementary Table 5 for a summary of all gene name abbreviations used in this Table and elsewhere in the paper. EAF is the allele frequency of the risk increasing allele.

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TABLE 3

Pathway Analysis

Ingenuity Canonical Pathways	Enrichment Analysis			
	Nominal p-value	**FDR q-value**	**Molecules**	**Pathway Size(N_{genes})**
Complement System	0.000012	0.0015	*CFI, CFH, C3, CFB**, *C2**,*C4A**, *C4B**	35
Atherosclerosis Signaling	0.00014	0.009	*PLA2G12A*, *APOC1***, *APOE***, *APOC2***, *APOC4***, *TNFSF14*, *COL10A1*, *PLA2G6*	129
VEGF Family Ligand-Receptor Interactions	0.0042	0.150	*VEGFA,PLA2G12A,PLA2G6*	84
Dendritic Cell Maturation	0.0046	0.150	*RELB*, *ZBTB12*, *DDR1*, *COL10A1*	185
Phospholipid Degradation	0.0058	0.151	*PLA2G12A*, *LIPC*, *PLA2G6*	102
MIF-mediated Glucocorticoid Regulation	0.0088	0.153	*PLA2G12A*, *PLA2G6*	42
Inhibition of Angiogenesis by TSP1	0.0093	0.153	*VEGFA*,*TGFBR1*	39
Fc Epsilon RI Signaling	0.0098	0.153	*VAV1*, *PLA2G12A*, *PLA2G6*	111
p38 MAPK Signaling	0.011	0.153	*PLA2G12A*, *TGFBR1*, *PLA2G6*	106

* *CFB*, *C2*, *C4A*, and *C4B* all flank rs429608 and thus counted as single hit when determining significance of enrichment.

** *APOC1*, *APOE*, *APOC2*, and *APOC4* all flank rs4420638 and thus counted as single hit when determining significance of enrichment.